REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Official Action dated April 25, 2003 and the phone interview with the Examiner on July 15, 2003. Applicants' representatives are scheduled to have a phone interview with the Examiner on August 28, 2003. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 8-9 are under consideration in this application. Claims 1-7 are being cancelled with prejudice or disclaimer. Claim 8 is being amended, as set forth in the above marked-up presentation of the claim amendments, in order to more particularly define and distinctly claim applicants' invention. Claim 9 is being added to recite another embodiment described in the specification.

Additional Amendments

The claims are being amended to correct formal errors and/or to better disclose or describe the features of the present invention as claimed. All the amendments to the claims are supported by the specification. Applicants hereby submit that no new matter is being introduced into the application through the submission of this response.

Formality Rejection

Claims 1-8 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. As indicated, the claims have been cancelled or amended as required by the Examiner. Accordingly, the withdrawal of the outstanding informality rejection is in order, and is therefore respectfully solicited.

Prior Art Rejections

Claims 1-7 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pat. No. 6,528,264 to Pal et al. (hereinafter "Pal") and U.S. Pat. No. 6,506,594 to Barany et al. (hereinafter "Barany"), and claims 1-2, 4, 6-7 were rejected as being anticipated by U.S. Pat. App. Pub. No. 2001/0049108 a1 to McGall et al. (hereinafter "McGall") In addition, claim 8 was rejected under 35 U.S.C. § 103(a) as being rendered obvious by Pal or Barany in view of an article by Wade (Organic Chemistry, 1991, pp.362,890, hereinafter "Wade"). The prior art references of U.S. Pat. App. Pub. No. 2002/0142339 to Bardhan et al. (hereinafter "Bardhan"), was cited as being pertinent to the present application. Further, a new reference, U.S. Pat. No. 5,688,642 to Chrisey (hereinafter "Chrisey") was mentioned by the Examiner on July 15, 2003 in a phone conversation. Specifically, in col. 15, lines 6-10, the Example 9 of Chrisey teaches "*A 1 mM solution of the heterobifunctional crosslinker SMPB {succinimidyl 4-(p-maleimidophenyl)butyrate} was prepared by dissolution in 100 .mu.l DMSO,* " which involves "products of hydrolysis of maleimide groups." These rejections have been carefully considered, but are most respectfully traversed.

As indicated, claims 1-7 are being cancelled with prejudice or disclaimer such that the relevant rejections become moot.

The nucleic acid arrays for detecting nucleic acids by hybridization of the invention, as now recited in claim 8, comprises (1) a plurality kinds of single-stranded nucleic acid probes for hybridizing to the nucleic acids, said nucleic acid probes being immobilized at different positions on a substrate surface by covalent bonds (page 17, lines 17-18); and (2) products of hydrolysis of maleimide groups present (e.g. "*hydrolyze a maleimide group, thereby introducing a functional group that can have negative charge in an aqueous solution to the surface of a region where no nucleic acid probe was immobilized.*" Example 6 on page 21, lines 8-11) on positions on the substrate surface where no nucleic acid probe is immobilized ("*nucleic acid probes are immobilized on a substrate, and then functional groups (denoted as "A" in FIG. 1) that can have* a *negative charge in an aqueous solution are introduced onto regions of the substrate on which no nucleic acid probe is immobilized*" page 12, lines 4-7; Abstract).

In other words, "products of hydrolysis of maleimide groups" are present on positions on the substrate surface where said nucleic acid probes are absent such that these positions are

negatively charged. Adsorption of the target nucleic acids are thus prevented from occurring on these positions due to electrostatic repulsion between these positions and negatively charged excess (un-hybridized) nucleic acids (page 17, lines 21-25). As a result, the detection noise of the target nucleic acids is reduced (page 1, lines 9-12).

Further, for those nucleic acid probes having thiol groups introduced thereinto (page 15, line 23) as recited in claim 9, a second functional group (crosslinker Y in Fig. 1 which directly links with the probes), i.e., maleimide groups, specifically react with the thiol groups of the probes as shown in Fig. 1 of the attached paper such that a large number of base-derived amino groups are present on the immobilized nucleic acid probes thereby increasing hybridization efficiency (page 9, lines 21-23 ; page10, lines 2-14). In this case, the "maleimide groups" and the "products of hydrolysis of maleimide groups" play two distinctive roles. While the "products of hydrolysis of maleimide groups" are used to repel excess (un-hybridized) nucleic acids, the "maleimide groups" function as crosslinkers for attaching nucleic acids to a solid support.

First of all, Applicants respectfully contend that neither Pal nor Barany, nor their combination as relied upon by the Examiner, teaches or suggests nucleic acid arrays having "products of hydrolysis of maleimide groups present on positions on the substrate surface where no nucleic acid probe is immobilized."

As admitted by the Examiner on page 10, line 1 of the outstanding office action, neither Pal nor Barany teaches using a functional group that is a "product of hydrolysis of a maleimide group". In other words, the prior art fails to teach using the "maleimide groups" as crosslinkers for attaching nucleic acids to a solid support. In other words, neither Pal nor Barany teaches using "products of hydrolysis of maleimide groups" to repel excess (un-hybridized) nucleic acids by having "products of hydrolysis of maleimide groups present on positions on the substrate surface where no nucleic acid probe is immobilized." At most, Barany teaches "blocking unreacted amino groups by acetylation or succinylation (rather than "product of hydrolysis of a maleimide group") to ensure a neutral or negatively charged environment that "repels" excess un-hybridized DNA (col. 25, lines 33-36)" .

Contrary to the Examiner's allegation on page 10 of the outstanding office action that maleic acid and succinic acid are similar to the claimed "products of hydrolysis of maleimide groups" (e.g., maleamic acid), the chemical structure of **maleamic** acid (See

BIQCONJUGATE Techniques, page 174) is very different form **maleic** acid (cis-HOOCCH=CHCOOH) or succinic acid (HOOCCH=CHCOOH). Even if maleic acid and succinic acid share similar structures such that they are functional equivalents as alleged, such a resemblance has nothing to do with maleamic acid thus has no bearing on any similarity between succinic acid and **maleamic** acid or between **maleic** acid and **maleamic** acid. The Examiner still bears the burden to prove any similarity between succinic acid and **maleamic** acid or between **maleic** acid and **maleamic** acid.

In addition, the fact that maleic and succinic also function as crosslinkers for attaching nucleic acids to a solid support as maleimide has NO bearing on the alleged similarity of the repelling function of the corresponding products of hydrolysis.

In addition, Barany discloses that nucleic acid probes are immobilized by reacting carboxylic acids on the substrate with amino groups at the end of the nucleic acid probes. Ideally, the amino groups at the end of the nucleic acid probes are bound to carboxylic acids on the substrate as shown in Fig. 2 of the attached paper. However, for an oligonucleotide of the nucleic acid probe with a large number of bases (A,T,G,C) as shown in Fig.3(a) of the attached paper, it has amino groups when bases comprise adenine, guanine and cytosine as shown in Fig.3(b) of the attached paper. Therefore, there are many cases wherein amino group of a base in the middle of the nucleic acid probes is bound to carboxylic acid on the substrate instead of the amino group at the end of the nucleic acid probe as shown in Fig.3(c) of the attached paper. As a result, the base to be used for the hybridization is bound to carboxylic acid on the substrate is not available for hybridization to the target nucleic acid thereby resulting in incomplete hybridization and thus reduced sensitivity. In contrast, a maleimide group of the present invention and a thiol group at the end of the nucleic acid probe are specifically reacted with each other as shown in Fig. 1 (claim 9), therefore obtaining high hybridization efficiency.

As to Chrisey, it fails to disclose any region on the slides having no nucleic acid probes immobilized thereon. Chrisey merely performs the following four steps in order: (A) preparing thiol-modified DNA oligomers (col. 14, line 15 – col. 15, line 5); (B) making slides with SMPB linkers (col. 15, lines 6-14); (C) adding thiol-modified DNA oligomers to bind with the crosslinkers (col. 15, lines 15-22); and (D) removing non-covalently bound DNAs from the slides (col. 15, lines 23-26).

Even if, arguendo, the relevant teaching in col. 15, lines 6-10, the Example 9 of Chrisey were

combined with the teaching in Barany of "*blocking unreacted amino groups by acetylation or succinylation* (rather than "product of hydrolysis of a maleimide group") *to ensure a neutral or negatively charged environment that "repels" excess un-hybridized DNA* (col. 25, lines 33-36)," the combination fails to provide products of hydrolysis of maleimide groups present on positions on the substrate surface where no nucleic acid probe is immobilized (the last sentence of claim 8).

Chrisey teaches a nucleic-acid-array making method by using thiol-modified DNA oligomers (example 9), wherein EDA and DETA films are prepared on slides, SMPB {succinimidly 4-(p-maleimidophenyl) butyrate} linkers are added, and then thiol-formed DNA oligomers are added. After thiol-formed DNA oligomers are added, they are covalently bounded to the SMPB linkers, but some of the oligomers are non-covalently bounded. Consequently, Chrisey treats the slides for 24 hours with 50mM Na-phosphate, 1M NaCl, ph 7.6 at 25°c (col.14, line 46 – col.15, line 36) to remove non-covalently bound DNAs. Treating the slides with Na-phosphate of **ph 7.6** (col. 15, line 23) is simply not enough to change maleimindo groups to the product of hydrolysis of maleiminde group. In the invention, the slides are treated by the EPPS buffer solution (alkali solution of ph 8.0) to present the product of hydrolysis of maleimide groups on the substrate surface where no nucleic acid probes is immobilized ("*The slide glass on which nucleic acid probes had been immobilized was immersed in an EPPS buffer solution (3-[4-(2-hydroxyethyl)-1-piperazi- nyl] propane sulfonate; 50 mM, pH8.0)*" p18, lines 21-24; Example 3, step (4); Example 1, steps (1)-(3)).

The ph 8.0 Na-phosphate mentioned in col. 14, line 64 shall not be confused with ph 7.6 Na-phosphate mentioned in col. 15, lines 25-26. The ph 8.0 Na-phosphate (col. 14, line 64) is used to prepare thiol-modified DNA oligomers in Step (A) by reducing "*the disulfide oligomer to its free thiol form [5'-(ACTG)5 -SH-3']* (col. 14, lines 65-66)", while the ph 7.6 Na-phosphate (col. 15, lines 25-26) is used to remove non-covalently bound DNAs from the slides in step (D). The ph 8.0 Na-phosphate (col. 14, line 64) has nothing to do with the SMPB linkers or to change maleimindo groups to the product of hydrolysis of maleiminde group as the EPPS buffer solution (ph 8.0) does in the invention.

Secondly, contrary to the Examiner's allegation that carboxylic acids remain on the positions that are not bound with the nucleic acid probes is negatively charged in Pal (page 5, lines 1-2; page 9, lines 7-8), Pal fails to specify the charging conditions of any N-hydroxysuceinimide ester that is not bound to a nucleic acid probe and remains as an intermediate. Pal discloses a method for immobilizing nucleic acid probes having modified

amino groups on a substrate having carboxylic acid incorporated thereinto, using N-hydroxysuceinimide (NHS) and dim ethyl arninopropyl-carbodiimide (EDC) (Fig. 4; col.-5, lines 36-45; col. 7, lines 22-33). NHS and EDC are used to react compounds having carboxylic acids with compounds having amino groups, and N-hydroxysuceinimide ester is produced as an intermediate in this reaction (See BIQCONJUGATE Techniques, page 174). When the N-hydroxysuceinimide ester is reacted with an amino group, an alcohol, and water, an amide compound, an ester, and a carboxylic acid are produced, respectively. Pal discloses "washing and blocking" after nucleic acid probes are immobilized (col.7, lines 30-31), but it does not disclose detailed conditions concerning the N-hydroxysuccimide ester that is not bound to the nucleic acid probe and remains as an intermediate. Therefore, it cannot be said that carboxylic acids remain on the region that is not bound to the nucleic acid probe and thus the region is negatively charged.

Thirdly, the Examiner's reliance upon the "common knowledge and common sense" of one skilled in the art for the motivation for combining the teachings in Pal, Barany, Wade and Chrisey did not fulfill the agency's obligation to cite references to support its conclusions. Instead, the Examiner must provide the specific teaching, e.g. *statements in the prior art,* of allegations of the combination on the record to allow accountability.

> *To establish a prima facie case of obviousness, the Board must, inter alia, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." Kotzab, 217 F.3d at 1370, 55 USPQ2d at 1317. .... Recently, in In re Lee, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002), we held that the Board's reliance on "common knowledge and common sense" did not fulfill the agency's obligation to cite references to support its conclusions. Id. at 1344, 61 USPQ2d at 1434. Instead, the Board must document its reasoning on the record to allow accountability. Id. at 1345, 61 USPQ2d at 1435.*
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> See In re Thrift, 298 F.3d 1357.

Such an obligation to provide specific teaching(s) also applies to other existing or future obviousness rejections.

Applicants contend that neither Pal, Barany, Wade and Chrisey, nor their combination teaches or discloses each and every feature of the present invention as disclosed in independent claim 8. As such, the present invention as now claimed is distinguishable and thereby allowable over the rejections raised in the Office Action. The withdrawal of the outstanding prior art rejections is in order, and is respectfully solicited.

In view of all the above, clear and distinct differences as discussed exist between the present invention as now claimed and the prior art reference upon which the rejections in the Office Action rely, Applicants respectfully contend that the prior art references cannot anticipate the present invention or render the present invention obvious. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicants' undersigned representative at the address and phone number indicated below.

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